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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MIEN-CHIE HUNG, YAN LI, and YONG WEN

Appeal 2008-2150
Application 10/816,698
Technology Center 1600

Decided: May 28, 2008

Before DONALD E. ADAMS, DEMETRA J. MILLS, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 12, 14-16, 21-26, 41, and 42. The remaining pending claims, claims 24 and 27-40 are withdrawn from consideration. We have jurisdiction under 35 U.S.C. § 6(b).

INTRODUCTION

The claims are directed to a method of inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject. Claim 12 is illustrative:

12. A method of inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject, comprising administering to the subject a mutant Bik polypeptide having an altered amino acid sequence, relative to SEQ ID NO:3, that comprises a substitution at least at a mutation at Thr33 or Ser35, wherein the mutant Bik polypeptide induces anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in the subject.

The Examiner relies on the following prior art references to show unpatentability:

Jaigi P. Mathai et al., *J. Biol. Chem*, BH3-only BIK Regulates BAX,BAK-dependent Release of Ca^{2+} from Endoplasmic Reticulum Stores and Mitochondrial Apoptosis during Stress-induced Cell Death, 25:23829-23836,(2005).

Y. Azar et al., *Apoptosis 2000,* GnRH-Bik/Bax/Bak chimeric proteins target and kill adnocarcinoma cells; the general use of pro-apoptotic proteins of the Bcl-2 family as novel killing components of targeting chimeric proteins, 5(6): 531-542, (2000).

James U. Bowie et al., *Science,* Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions 247(4948): 1306-1310, (1900).

The rejections as presented by the Examiner are as follows:

1. Claims 12, 14-16, 18-26, 41, and 42 stand rejected under the written description provision of 35 U.S.C. § 112, first paragraph.

2. Claims 12, 14-16, 18-26, 41, and 42 stand rejected under the enablement provision of 35 U.S.C. § 112, first paragraph.

We affirm.

DISCUSSION

Claim Construction:

Claim 12 is drawn to a method of inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject. The claimed method comprises administering to a subject a mutant Bik polypeptide.

Claim 12 defines the mutant Bik polypeptide as having an altered amino acid sequence, relative to SEQ ID NO: 3, that comprises a substitution at least at a mutation at Thr33 or Ser35.

In addition, claim 12 requires that the mutant Bik polypeptide induces anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in the subject.

The polypeptide set forth in SEQ ID NO: 3 is 160 amino acids in length. Thus claim 12 reads on a genus of mutant Bik polypeptides that comprise from 1 to 160 amino acid substitutions of SEQ ID NO: 3. Further each member of the genus encompassed by claim 12 must induce anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject.

Written Description:

Claims 12, 14-16, 18-26, 41, and 42 stand rejected under the written description provision of 35 U.S.C. § 112, first paragraph.

As discussed above, claim 12 reads on a genus of mutant Bik polypeptides that comprise from 1 to 160 amino acid substitutions of SEQ ID NO: 3[1]. In addition, each member of the genus encompassed by claim 12 must induce anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject.

As Appellants point out, their specification provides three examples of a polypeptide that falls within the genus of claim 12:

1. SEQ ID NO: 9, which comprises mutations at both Thr33 and Ser35;

2. SEQ ID NO: 7, which illustrates a mutation at Thr33; and

3. SEQ ID NO: 8, which illustrates a mutation at Ser35 (App. Br. 11[2]).

We also recognize that Appellants' Specification discloses:

a. sets of amino acids that are considered biologically functional equivalents according to the claimed invention (Spec. ¶ 0079; App. Br. 10),

b. that "[i]t is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity" (Spec. ¶¶ 0081-0084; App. Br. 10),

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[1] According to the Examiner, claim 12 is "broadly drawn to a mutant Bik polypeptide having *any* altered amino acid sequence, relative to SEQ ID NO:3, that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35}" (Ans. 12-13).

[2] The Appeal Brief (App. Br.) is not paginated. Accordingly, we refer to page numbers as if the App. Br. was paginated consecutively beginning with the first page as number 1.

c. that Table 1 of the Specification provides a codon table for "all standard amino acids" (App. Br. 11; Reply Br. 3[3]; Spec. ¶ 0073), and

d. mutagenesis methodology (App. Br. 10; Reply Br. 3; Spec. ¶¶ 0221-0226).

There is, however, no requirement in Appellants' claim that substitutions be made with functionally equivalent amino acids or amino acids that have a similar hydropathic index. That the genetic code is degenerate, as exemplified by Appellants' Table 1, does not support a finding that any amino acid in SEQ ID NO: 3 may be substituted for any other amino acid, while retaining at least one stated activity as is set forth in claim 12.

Further, Appellants fail to direct our attention to any portion of their Specification or knowledge in the art that identifies a particular structure of SEQ ID NO: 3 that can be varied while retaining the ability of the polypeptide to induce anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject. As the Examiner explains "neither the claims nor the specification teach the amino acids critical to the claimed function of the broad genus of mutant Bik polypeptides" (Ans. 16).

Thus, while Appellants' Specification demonstrates that Appellants' were in possession of three species within the claimed genus (SEQ ID NOs: 7-9), one of ordinary skill in this art would not be able to identify, without further testing, which additional polypeptides encompassed by the claimed invention would have the required activity of inducing anti-tumor activity,

[3] The Reply Brief (Reply Br.) is not paginated. Accordingly, we refer to page numbers as if the Reply Br. was paginated consecutively beginning with the first page as number 1.

anti-cell proliferation activity, and/or pro-apoptotic activity in a subject. We are not persuaded by Appellants' assertion that the critical structure is represented by alterations at Thr^{33} or Ser^{35} (Reply Br. 4) and therefore "[i]t is not necessary to teach other amino acids as being critical to the activity, or not, because the critical ones have already been disclosed" (Reply Br. 5).

Appellants appear to miss the point. They have exemplified three species encompassed by the claimed genus which describe alterations at Thr^{33} or Ser^{35} where the remainder of the polypeptide retains the sequence of SEQ ID NO: 3. There is, however, no evidence on this record that the substitution of, for example, all 160 amino acids of SEQ ID NO: 3 with any other amino acid, as is encompassed by claim 12, would retain the activity required by claim 12. The identification of two "critical" amino acids in a 160 amino acid sequence is not sufficient where a substitution of every amino acid in the claimed 160 amino acid polypeptide is permitted. What remains undisclosed on this record is which of the many different mutant polypeptides encompassed by the claimed genus would retain the activity required by claim 12.

Describing a claim to a method requires describing the compounds used in the method. *See University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004). A chemical genus can be described by structural description of a representative number of the species within the genus or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997). The structural description does not necessarily require disclosure of the compound's complete chemical structure:

> the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics.'

Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964, (Fed. Cir. 2002) (emphasis omitted, alteration original).

For the reasons set forth above, here as in *Rochester*, Appellants' Specification does not disclose *which* of the many polypeptides encompassed by claim 12 have the recited activities. The *Rochester* court held that such a disclosure does not adequately describe a genus of compounds required to practice a claimed method. While Appellants disclose three species within the claimed genus, Appellants have not demonstrated that these three species are representative of the entire genus of compounds having the recited activities or that it shares "structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Cf. Eli Lilly*, 119 F.3d at 1569. Further, while claim 12 requires that amino acid modifications are made relative to SEQ ID NO: 3, there is no requirement in the claim that any structural feature of SEQ ID NO: 3 be retained. Simply stated Appellants have failed to establish a correlation between the structure and function of the claimed polypeptides that is common to the members of the genus.

Accordingly, we affirm the rejection of claim 12 under the written description provision of 35 U.S.C. § 112, first paragraph. Claims 14-16, 18-26, 41, and 42 fall together with claim 12.

Enablement:

Claims 12, 14-16, 18-26, 41, and 42 stand rejected under the enablement provision of 35 U.S.C. § 112, first paragraph.

According to the Examiner

> [o]ne cannot extrapolate the disclosure of the specification to the enablement of the claims because the claims are broadly drawn to a genus of mutant Bik polypeptides having any altered amino acid sequence, relative to SEQ ID NO:3, that comprise a substitution at least at a mutation at Thr^{33} and Ser^{35} . . . wherein it cannot be predicted that the broad genus of mutant Bik polypeptides will function as claimed.

(Ans. 8.)

In this regard, the Examiner finds that Bowie teaches "that an amino acid sequence encodes a message that determines the shape of a protein and determines the ability of said protein to fold into unique three-dimensional structures that allows them to function" (Ans. 11). According to the Examiner, Bowie teaches "that certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitution or no substitutions (*id.*). The Examiner finds that "neither the specification nor the art of record provide teachings that provide information about the effects any altered amino acid sequence relative to SEQ ID NO:3 and any amino acid substitution at positions Thr^{33} and Ser^{35} would have on the activity of a mutant Bik polypeptide" (*id.*). According to the Examiner

> [t]his information appears to be critical because the art recognizes . . . that it is the protein sequence that determines the three dimensional shape of a protein and suggests that the three-dimensional structure of the protein molecule may be essential for the protein's function and ability to be modulated. Thus, in

> the absence of guidance in the Specification, the effects of the undefined amino acid substitutions, it cannot be predicted and one could not determine how to practice the claimed invention or predict which of the whole universe of broadly claimed mutant Bik polypeptides having any altered amino acid sequence relative to SEQ ID NO:3 and comprising any substitution at positions Thr^{33} and Ser^{35} would function as claimed with a reasonable expectation of success.

(Ans. 11-12.)

In response, Appellants assert that "[m]ethods of mutagenesis are well known to those of skill in the art" and are "described in the specification" (App. Br. 14). We agree, but note that this does not address the issue before this panel. To the contrary, the issue before this panel is whether a person of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation. More specifically, the issue is whether it would require undue experimentation for a person of ordinary skill in the art to start with SEQ ID NO: 3 as a reference sequence and then randomly modify every amino acid in this sequence with another amino acid and still expect to induce anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject. Merely acknowledging that methods of mutagenesis are known in the art does not address this issue. Further, Appellants' disclosure of "functionally equivalent" amino acids and amino acids that exhibit similar hydrophobic indices is not satisfactory because the claimed invention is not limited to amino acid substitutions that are functionally equivalent or share similar hydrophobic indices. Accordingly, we are not persuaded by Appellants' assertion to the contrary (App. Br. 14).

Further, for the foregoing reasons we disagree with Appellants' assertion that "no more than routine screening would be required to practice

the full scope of the claimed invention" (App. Br. 14). The claimed invention reads on a polypeptide that is modified by substituting any amino acid for every one of its 160 amino acids, while at the same time retaining the ability to induce anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject. Stated differently, the claimed invention reads on a polypeptide that consists of 160 consecutive proline residues. There is no disclosure in the instant Specification that would lead a person of ordinary skill in the art to reasonably expect that such a polypeptide would be capable of inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject. Accordingly, we disagree with Appellants' assertion that "Appellants have disclosed the critical alterations, provided a representative sequence, provided exemplary alterations, and demonstrated how to test for the activity" and therefore undue experimentation would not be required (Reply Br. 7). Presumably the critical alterations to which Appellants refer are Thr^{33} and Ser^{35}, the representative sequence is SEQ ID NO: 3, and the exemplary alterations are functionally equivalent amino acids or amino acids that share similar hydrophobic indices. Claim 12 is not, however, limited to modifications of only Thr^{33} and/or Ser^{35}; or alterations that are limited to the substitution of functionally equivalent amino acids or amino acids that share similar hydrophobic indices. Instead, the claimed invention encompasses substitutions of all 160 amino acids of the polypeptide.

The enablement requirement of 35 U.S.C. § 112, first paragraph, requires that the patent Specification enable those skilled in the art "to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk. A/S*, 108 F.3d 1361,

1365 (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). To satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, a patent application must adequately disclose the claimed invention so as to enable a person skilled in the art to practice the invention at the time the application was filed without undue experimentation. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371-72 (Fed. Cir. 1999).

For the foregoing reasons, we find that it would require undue experimentation for a person of ordinary skill in the art to practice the full scope of the claimed method which requires the administration of a mutant Bik polypeptide, wherein the Bik polypeptide sequence has a substitution ranging from at least Thr^{33} or Ser^{35} to all amino acids relative to the sequence set forth in SEQ ID NO: 3 while retaining the ability to induce anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject.

Having found that Appellants' have not met their burden of providing an enabling disclosure for their claimed invention, we need not reach the merits of the Examiner's additional rationale relating to lack of enablement, which is based on the Mathai and Azar references; or Appellants' response thereto.

Accordingly, we affirm the rejection of claim 12 under the enablement provision of 35 U.S.C. § 112, first paragraph. Claims 14-16, 18-26, 41, and 42 fall together with claim 12.

CONCLUSION

In summary, we affirm the rejections of record.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

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